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Research paper

Restriction of non-opioid analgesics sold over-the-counter in Denmark: A national study of impact on poisonings

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A B S T R A C T

Objective: Self-poisoning with non-opioid analgesics presents a growing challenge to health care providers. We aimed to assess the impact of an 18-year age restriction of OTC sales and a pack size restriction of non-opioid analgesics sold OTC in pharmacies on hospital-treated poisonings and poisoning severity measured using biomarkers.

Methods: We applied a before and after design using interrupted time series analysis. Data on all poisonings recorded as hospital admissions were obtained during 2002–2015 and biochemical parameters from laboratory databases during 2011–2015, both covering the entire Danish population.

Results: The age restriction was followed by a 17% level reduction in admissions for non-opioid analgesic poisoning among young people age 10–17 years (RR 0.830; 95% CI 0.697–0.988; $p < 0.036$). After the pack size restriction, an instant level reduction of 18.5% (RR 0.815; 95% CI 0.729–0.912; $p < 0.001$) was observed for the entire population. A 27% decrease in the number of poisonings with alanine transaminase levels (ALT) ≥ 210 U/L was observed (RR 0.734; 95% CI 0.579–0.931; $p = 0.011$) followed by 40% decrease in biomarkers indicative of liver failure (RR 0.597; 95% CI 0.421–0.847; $p = 0.004$). We also observed similar reductions for other poisonings such as psychotropics.

Limitations: Although declines in poisonings were observed after implementation of means restrictive measures, a causal link cannot be inferred.

Conclusion: Age and pack size restriction were assiociated with a reduction in the numbers of poisonings. This was also observed for pharmaceutical poisonings in general, which might suggest a non-specific or spill-over effect.

1. Introduction

Emergency department and intensive care units treat an increasing number of patients who have self-poisoned with non-opioid analgesics (Gedeborg et al., 2017; Morthorst et al., 2016). High prevalence of self-poisoning has been reported among depressed patients (Bachmann, 2018; Bertolote et al., 2004) as well as in young, depressed populations (Fleming et al., 2007; Qin et al., 2018). Paracetamol is particularly frequently used in deliberate self-harm incidents involving adolescents and young adult women (Carroll et al., 2015; Geulayov et al., 2016). Links between availability of non-opioid analgesics over-the-counter (OTC) and hospital presentations with non-opioid analgesic poisoning as well as deaths have been noted in European studies (Gedeborg et al., 2017; O'Rourke et al., 2002). Among the non-opioid agents, paracetamol is sold OTC in most countries and, by large, ingested safely. However, for this specific agent doses exceeding daily recommendations bear the risk of hepatotoxicity (Bunchorntavakul and Reddy, 2013). Given the risk of acute liver failure due to paracetamol and multi organ failure also following severe salicylate poisonings and the consequential substantial health care burden of this (Bromer and Black, 2003), the need for restrictions on non-opioid analgesic availability seems sensible but remains disputed (Bateman, 2014; Hawton, 2002).

Many European countries, including the United Kingdom (UK), France, Ireland, and Sweden, have restricted pack sizes of non-opioid analgesics sold OTC in pharmacies (Morthorst et al., 2018). However,

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few evaluations of these efforts have been conducted (Bateman, 2009; Gunnell et al., 2000). One exception is the UK pack size restriction that was linked to fewer deaths by suicide due to paracetamol, admissions to liver units and referrals to hepatic and transplant units (Hawton et al., 2004; Hughes et al., 2003). Moreover, as many as 990 deaths might have been prevented during the subsequent 11 years (Hawton et al., 2013).

Conflicting findings have been reported for evaluations of pack size restrictions based on biomarkers (Prince et al., 2000; Robinson et al., 2000; Sheen et al., 2001); local studies examining the impact on blood concentrations and biomarkers, such as liver enzymes (ALT and INR), have shown reductions in severity of poisonings (Hawton et al., 2001; Robinson et al., 2000). Some have reported slightly higher maximum values of creatinine, a biomarker for kidney failure, and prothrombin time post intervention (Prince et al., 2000) in spite a decrease in rates of severe paracetamol poisonings as well as a reduction in median grams ingested; while others found increased numbers of paracetamol tests with values above 1.3 mmol/l (Sheen et al., 2001). Changes in severity of non-opioid poisonings were observed as a decrease in mean levels of salicylates and prothrombin ratios but no change in paracetamol levels after the legislative change (Hawton et al., 2001). However, findings were all restrained by short follow-up periods, some covering small catchment areas, and few observations. To sum up, studies showed fewer poisonings but opposite findings in relation to the severity of these.

To limit the availability of non-opioid analgesics, two legislative measures have been implemented in Denmark: an 18-year age purchase restriction in 2011 and a pack size restriction for OTC sales in 2013. Prior to the pack size restriction, as many as 300 tablets of paracetamol or Ibuprofen were available OTC in pharmacies, while packages with 10 tablets of paracetamol (500 mg) or Ibuprofen (200 mg) were available in non-pharmacy outlets. In Denmark, sales of mild analgesics correspond to 105 and 102 Defined Daily Doses (DDD by WHO), yearly per 1000 inhabitant in 2013 and 2015, respectively (Data, 2020; Schmidt et al., 2016).

The aim of this study was to evaluate the impact of these two interventions on intentional and accidental self-poisonings in patients treated at Danish hospitals. Secondly, we aimed to investigate the severity of poisonings on biochemical and hepatic parameters by comparing blood tests before and after the legislation on OTC sales in pharmacies. To our knowledge, the current study is the first to combine nationwide hospital data as well as laboratory data to assess trends in poisonings with non-opioid analgesics.

2. Methods

2.1. Setting and study population

A pre-post design was employed. The study period was from 2002 to 2015 and the population were patients treated for poisonings identified with their Danish civil registration number (CPR); the CPR number is unique and assigned to all Danish residents upon birth or immigration (Pedersen, 2011). Universal tax paid health care in Denmark is freely available for all people having a CPR number allowing for linkage of national hospital data through the National Patient Register and the Psychiatric Central Research Register (Erlangsen and Fedyszyn, 2015). These have since 1994 applied the International Classification of Diseases 10th (IDC-10) and since 1995 included contacts with emergency departments and outpatient services.

National biochemical data were obtained by linking five regional laboratory databases capturing blood samples taken routinely during hospitalization for poisonings.

2.2. Exposures

Two legislative measures affecting the availability of non-opioid analgesics were implemented in Denmark. First, an age restriction was introduced to ensure that only persons aged 18 years or older could purchase non-opioid analgesics OTC in both pharmacies and non-pharmacy outlets on March 7th, 2011. In pharmacies, unrestricted amounts were available, while a maximum of 10 tablets could be obtained in non-pharmacy outlets (2017c). Second, on September 30th, 2013, OTC sales of non-opioid analgesics were restricted to 20 tablets in pharmacies.

2.3. Outcomes

2.3.1. Register data

Our primary outcome of poisonings was defined as presentations to emergency departments or hospitals with a poisoning by non-opioid analgesics (ICD-10: T39 and X60), including both accidental and intended poisonings of paracetamol, NSAIDs and aspirins (acetylsalicylic). We collected information on presentations to both somatic and psychiatric hospitals where a main or sub-diagnosis had indicated a poisoning; a joint measure to elude under registration of intentional self-poisoning (Morthorst et al., 2016).

A separate category of *other poisonings* covered all other pharmacological poisonings (ICD-10: T38 and T41-T50), including intended self-poisoning by psychotropic drugs, drugs affecting the autonomic nervous system, and other unspecified agents (ICD-10: X61, X63, X64) as well as accidental poisonings. Given that opiate poisoning (ICD-10: T40) can be related to substance misuse, it is often difficult to determine the underlying intention, Therefore, this diagnosis was omitted. A category of *violent methods,* consisting of suicide attempts by hanging, drowning, firearms, explosives and fire, sharp objects, moving objects, and unspecified methods (ICD-10: X70-X84), was also identified. The definitions of intentional and unintentional self-harm are based on previous studies (Gasse et al., 2018; Morthorst et al., 2016), which partially examined these as joint measures and likewise were based on National Danish Registers with high validity (Schmidt et al., 2019). The most frequently used analgesics in Denmark paracetamol, aspirin and ibuprofen exist, apart from single preparations, only in combination with low doses of caffeine and codeine as OTC products, hence without risk of influencing potential toxic cases.

Data on deaths involving non-opioid poisonings, suicides, and toxic liver disease were obtained from the Cause of Death Registry.

2.3.2. Laboratory data

Biochemical data from laboratory tests performed for individuals recorded with a hospital contact due to a non-opioid analgesic poisoning (ICD-10: T39, X60), as defined above, were collected for the period 2011–2015. As a part of the regular clinical workup on non-opioid poisonings, certain standard tests are administered to determine poison risk, namely plasma concentrations of paracetamol and salicylate (mmol/l), liver and renal function measures of alanine transaminase (ALT; U/L), coagulation factors II, VII, X (INR or; prothrombin time), total bilirubin level (TBL; μmol/l) and creatinine (μmol/l) (Grann et al., 2011). Peak values, i.e. the highest level measured during admission, were preferred as measures as they provide indication of severity and prognostic values. Using general guidelines (2017a; Pakravan et al., 2008; Temple, 2006), we developed a set of hierarchical severity measures to denote risk of toxicity and organ impairment, for instance, toxic creatinine levels, which were indicative of a poor prognosis in paracetamol poisonings. The toxic levels of paracetamol concentration and salicylate were considered as 1.3 mmol/l and 3.5 mmol/l, respectively. The risk levels applied were: risk level I (ALT ≥ 210 U/L), level II (ALT ≥ 1000), level IIIa + b (INR ≥ 1.54 ratio or TBL ≥ 50 μmol/l), level IV (ALT ≥ 1000 and paracetamol ≥ 1.3 mmol/l) and level V (ALT ≥ 1000 and INR ≥ 1.54 ratio or ALT ≥ 1000 and TBL ≥ 50 μmol/l), ranging from moderate to severe hepatoxicity with poor prognosis). Please see the eText box. The lower reference value was used, when values of blood concentrations were

listed with a sign (>) instead of a numeric value. We excluded cancelled tests and results where jaundice (icterus) or haemolysis had been recorded as text opposite to numbers. Biochemical data were available for 20,470 episodes of non-opioid analgesics poisonings (T39) and 3912 episodes of intentional self-poisonings (X60). The total number of peak values varied from 9095 for salicylate to 16,644 for ALT.

2.4. Ethical considerations

The study was approved by the Danish Data Protection Agency (RHP-2013-022) and the Danish Health Authorities (3-3013-494/1).

2.5. Interrupted time series analysis

We applied a combination model of interrupted time series analysis to assess whether the interventions might be linked to 1) an instant level change (as an immediate effect), 2) trend change (a possible suggesting that smaller packages being kept in households), or 3) a combination of both (Lopez Bernal et al., 2016). Quasi-Poisson regression models were fitted to number of monthly events. Since October 2001, small packages of non-opioid analgesics (5 gs) have been available in other outlets than pharmacies; hence, the study period 2002–2015 was selected. Best-fitted models were constructed using the following intervals: *pre-intervention* (January 2002–February 2011), *interim period* (March 2011–September 2013), and *post intervention* (October 2013–December 2015). Data on biomarkers were divided into 33 months before and 27 months after the pack size restriction where data were available. The trend within each interval was estimated by rate ratios [RR] comparing the relative change in rates per year with 95% confidence intervals (estimated from monthly data) (Humphreys et al., 2017). Ratios of rate ratios [RRR] were employed to assess the relative difference in trends in different intervals. The model allowed for an instant level change quantified using rate ratio to compare the rate after to before the interventions. Residual autocorrelation was assessed by examining deviance residual plots and the partial autocorrelation functions. We found no evidence for autocorrelation. Adjusting for seasonal variation by using Fourier terms did not improve the model fit and was omitted (Lopez Bernal et al., 2016). As correction for multiple testing was not performed, we opted for complete transparency of testing by listing all calculated estimates with their confidence intervals (eTables). Data management was handled in SPSS 22 and SAS 9.4, while analyses were performed using the R software.

3. Results

3.1. Hospital presentations

During 2002 to 2015, a total of 56,586 individuals, including 42,762 women (mean age 29.7 years; SD 17.4) and 15,824 men (mean age 36.0 years; SD 18.9) presented to hospital with either intentional or accidental non-opioid analgesics poisonings.

As seen in Fig. 1a, there was no level change observed for non-opioid analgesics poisonings after the age restriction on OTC sales ($p = 0.244$). However, a subsequent decrease in trend was noted ($p = 0.015$) (eTable 1). At the time of the pack size restriction, an instant level reduction in number of non-opioid poisonings per year of 18.5% (RR 0.815; 95% CI 0.729–0.912; $p < 0.001$) was estimated.

The trend in other poisonings showed significant level reductions of 10% (RR 0.899; 95% CI 0.856–0.945; $p < 0.001$) and 11% (RR 0.887; 95% CI 0.825–0.954; $p = 0.001$) after the age and pack size restriction, respectively. We found no change in violent methods when comparing pre-intervention versus interim period ($p = 0.675$) trends; however, the pack size restriction was followed by a 28% level reduction (RR 0.719; 95% CI 0.580–0.890) in violent methods.

When stratifying by age, we found that the age restriction in mild analgesic sales was primarily linked to a significant instant level change of 17% reduction in non-opioid analgesic poisonings (RR 0.83; 95% CI 0.697–0.988; $p = 0.036$) among those aged 10–17 years, at whom the intervention was directed. In addition, a significant decrease in other poisonings of 18% was observed among adolescents (RR 0.822; 95% 0.691–0.978; $p = 0.027$) (Fig. 2b). No significant change was noted for the older age group. As seen in Fig. 2a, a significant level change in non-opioid analgesic poisonings was noted among adults after the pack size restriction (RR 0.867; 95% CI 0.781–0.962; $p = 0.007$). This was also the case for violent methods in the adult population (RR 0.716 0.572–0.896; $p = 0.004$) (Fig. 2c).

3.2. Biochemical parameters

3.2.1. Severity measures of poisonings

A significant change was noted in blood test results for paracetamol concentrations above the toxic threshold of 1.3 mmol/l after the pack size restriction (test for equal trends: $p < 0.001$) (Fig. 3a and b, eTable 2), while this was not the case for the salicylates level, by the toxic threshold of 3.5 mmol/l (test for equal trends: $p = 0.91$). The Figs. 4a-g illustrate the number of poisonings with peak values above a threshold of toxicity and estimated events before and after the pack size restriction. Concerning risk of renal impairment, the yearly trend in the rate of creatinine levels above 120 μmol/l was 1.240 (95% CI 1.114–1.381) changing to 0.795 (95% CI 0.676–0.937) after the pack size restriction (test for equal trends: $p < 0.001$) (Fig. 4e).

For *risk level I*, there was a 26.6% level drop in the rate of ALT tests with values above 210 U/L (RR 0.734; 95% CI 0.579–0.931; $p = 0.011$), suggesting fewer severe non-opioid analgesic poisonings after the intervention. Regarding risk level II, we observed an instant reduction of 31.4% in the rate of tests with ALT values above 1000 U/L (RR 0.686, 95% CI 0.494–0.953; $p = 0.025$). For INR and TBL values above toxic threshold (*risk level IIIa-b*) no significant difference was detected.

Regarding poisonings with risk of liver injury (*risk level IV*), there was no evidence of a difference in trends nor level change after the intervention. For *risk level V,* severe hepatoxicity with poor prognosis, we noted a significant instant level reduction of 40.3% (RR 0.597, 0.421–0.847; $P = 0.004$) following the pack size restriction.

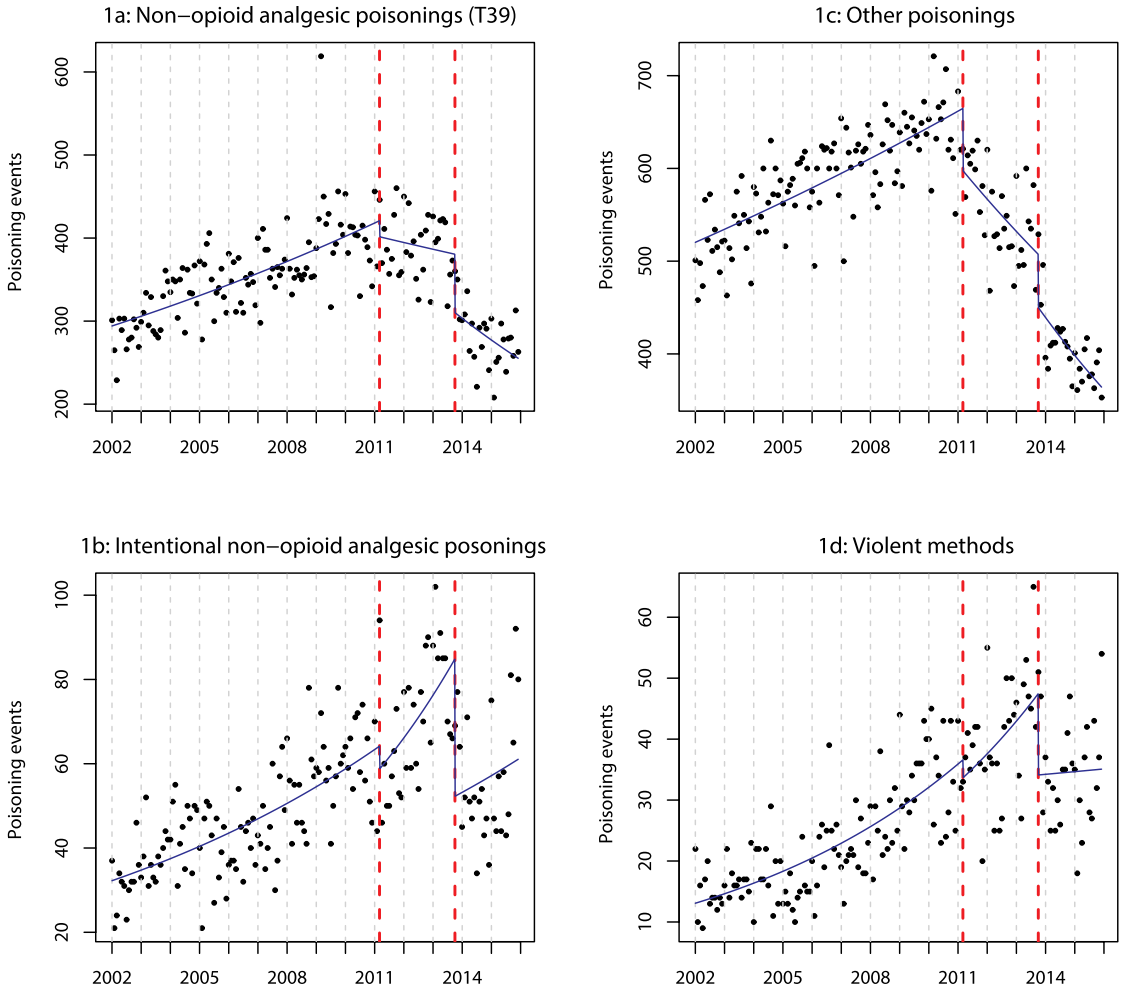
3.2.2. Deaths

The number of deaths due to accidental poisoning and suicides by non-opioid analgesics did not change when comparing the 15 months before and after the pack size restriction (accidental poisoning: 5 versus 5 deaths; suicide: 9 versus 10 deaths). Suicides involving intentional self-poisoning by unspecified drugs were 42 versus 39 deaths before and after, respectively. Hence, the numbers of suicide deaths and fatal poisonings were too small for meaningful analysis.

4. Discussion

Using nationwide hospital and biochemical data, we found that the monthly number of non-opioid analgesic poisonings decreased significantly after both the age and pack size restriction. We also found that there were fewer severe poisonings with risk of liver injury.

We found a 18.5% reduction in the number of non-opioid analgesic poisonings per month following the pack size restriction. This is supported by reductions between 11% and 31% in emergency department visits and admissions due to paracetamol poisoning noted in previous studies (Hawton et al., 2001; Hughes et al., 2003) with even larger



[1]The first red dotted line represents the age restriction (March 2011) and the second the pack size restriction (September 2013).

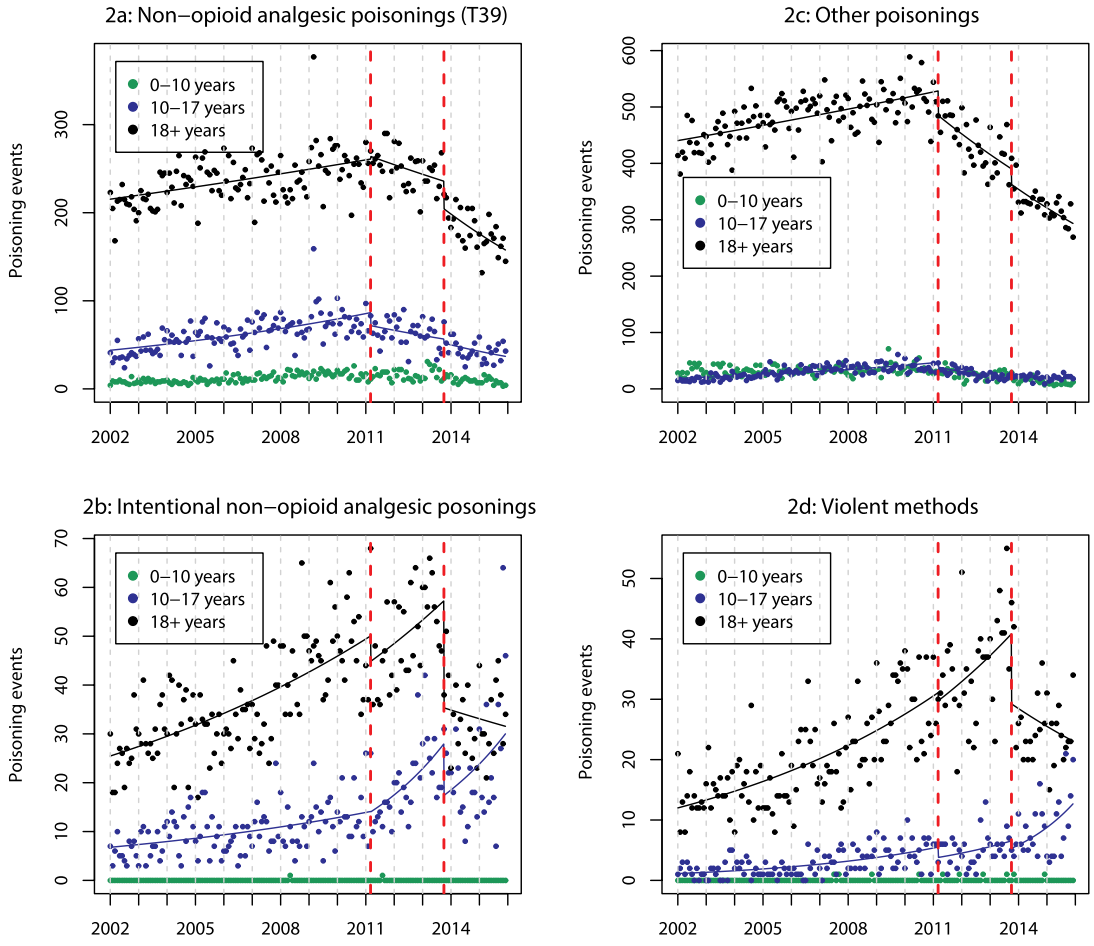
Fig. 1. a–d Time-series-analysis of primary outcome as hospital contacts for non-opioid analgesics poisonings, intentional non-opioid analgesics poisonings, violent methods and other poisonings during 2002–2015[1] .

reductions for severe poisonings. (Hawton et al., 2004; Turvill et al., 2000). The present study is seemingly the first evaluation of an implemented age restriction.

The few studies, in which sub-group analysis have been conducted by age, sex or drugs, have reported inconsistent results (Bateman et al., 2003, 2006). We found a significant reduction in non-opioid analgesics poisonings (T39) among youth aged 10–17 years following the age restriction. Comparable effects have been reported for other drug poisonings, such as anti-depressants, opioids and benzodiazepines (Bateman et al., 2003; Turvill et al., 2000); although one study found a significant increase in antidepressant and opioid poisonings, suggesting a shift towards other poisonings (Bateman et al., 2003). In Denmark, however, a decrease by poisonings by agents only available on prescription occurred among adolescents following the age restriction. The general decrease of all pharmaceutical poisonings among younger age groups could be suggestive of a public health 'up-stream' preventive effect of both legislative changes. Although the option of method substitution has been hypothesized, it has not previously been examined whether people at risk might divert to violent methods. Due to small numbers, it cannot be determined nor excluded whether a substitution to violent methods occurred among teenagers. As cutting was included in this category, this could reflect an increasing tendency to use sharp objects.

A decreasing trend in poisonings resulting in high blood levels of paracetamol, i.e. indicative of toxicity, was noted after the pack size restriction, while no trend differences or level change was found for events with potential toxic salicylate concentrations. Comparable findings have previously been shown for paracetamol levels (Robinson et al., 2000) while early studies noted a decrease in salicylate levels (Hawton, 2002; Hawton et al., 2001). In one study, paracetamol concentrations remained unchanged (Sheen et al., 2001). Although drug concentrations should be cautiously interpreted when not related to time of ingestion, our findings suggest that the pack size restriction led to a reduction in the number of severe poisonings with risk of liver injury.

A previous study, which assessed impact of paracetamol pack size restriction on biomarkers of liver function by examining median concentrations of liver enzymes 24–48 h after attending hospital, found no change in ALT levels associated with paracetamol poisonings (23 before vs. 23 U/L after) (Robinson et al., 2000). In this perspective, the decreased rate of poisonings with risk of renal impairment, liver injury and severe hepatotoxicity noted in the present study is intriguing. Also, the significant level change noted for ALT values above 210 and 1000 U/L immediately following the intervention and the 40% level decrease in the number of events of the proxy for severe hepatotoxicity provides robust evidence that fewer toxic test results were observed



[1] The first red dotted line represents the age restriction (March 2011) and the second the pack size restriction (September 2013).

Fig. 2. a–d Time-series-analysis of primary outcome as hospital contacts for non-opioid analgesics poisonings, intentional non-opioid analgesics poisonings, violent methods and other poisonings during 2002–2015 by age groups[1].

among patients treated after the pack size restriction; i.e. indicative of lower levels of toxicity for poisonings treated in hospital.

It has been suggested that means restrictions might be followed by method substitution. In this study, we did not find affirmative signs of method substitution; on the contrary, we found a decreasing trend in other poisonings. As this decrease was viewed to be unrelated to the examined interventions, other explanations were sought. However, authorities responsible for registers confirmed that registration procedures had not been changed during the study period. Also, national changes in doses of prescribed medication could not explain the observed decline in other poisonings. Likewise, a potential positive impact related to the establishment of the Danish Poison Information Centre has not been demonstrated. Clinical health care providers may have intensified their focus on preventing poisonings in general and screening for suicide risk during admission (Sakinofsky, 2014) but this does not seem to fully explain the trend. It could be a spill-over effect, for instance, through increased awareness regarding safe storage of household medication; similar effects have previously been noted for other forms of means restriction, such as self-poisoning (Morgan et al., 2005), jumping from high places (Reisch and Michel, 2005), and other hotspot interventions (King and Frost, 2005). It is, however, possible that the reductions we observed for other poisonings are the result of factors unrelated to the intervention, such as other prevention policies and socio-demographic changes, hence a potential source of confounding.

OTC sales of the examined drugs both in- and outside pharmacies have previously been discussed (Bateman, 2009, 2014). A recent investigation of the association between sales of mild analgesics in pharmacy and non-pharmacy outlets and the frequency of calls to poison information centers, as a proxy for the severity of poisonings by these agents, found that the lowest rates of paracetamol related calls were found in those European countries where sales outside pharmacies were not allowed ($p = 0.02$) compared to those allowing such sales in supermarkets and at gas stations (Morthorst et al., 2016). However, lliberalisation outside pharmacies, often implies even smaller packages sold, as is the case in Denmark. An argument to support even fewer household stocks.

5. Limitations

The major strengths of our study are the access to the national hospital data and comprehensive laboratory data. Although the single ICD-codes used here have not been validated, they have previously been validated as joint measures (Gasse et al., 2018) to elude a risk of

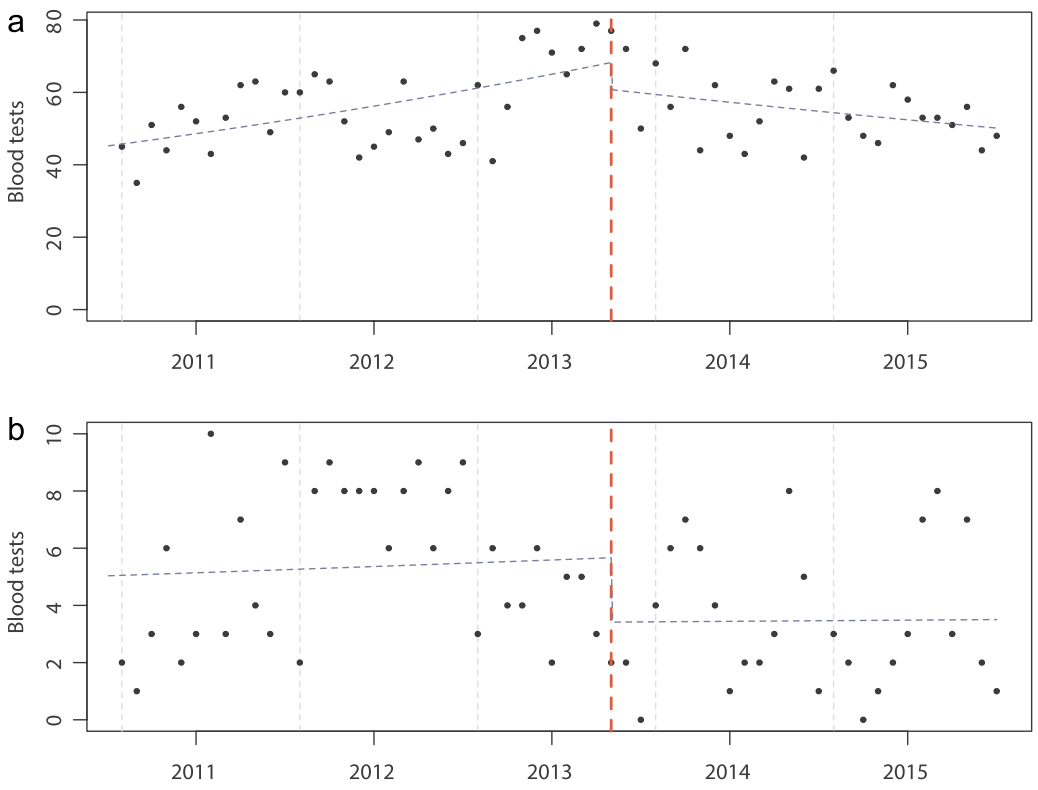


Fig 3. Plasma paracetamol toxic level _ 1•3 mmol/l.
The red dotted line represents the pack size restriction (September 2013).
Salicylate toxic level _ 3•5 mmol/l.
The red dotted line represents the pack size restriction (September 2013). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

under registration of intentional self-harm. The ICD-codes used in the psychiatric and somatic registers are generally considered as valid and have been tested for several different disorders (Schmidt et al., 2019).

The variety of laboratory tests and measures are unique and strengthens the reliability of our findings. The inclusion criteria of both accidental and intentional poisonings would capture all relevant cases. The fact that there are no user fees associated with laboratory tests and the electronic management of test results further enhances the validity of the biochemical databases. Internal validity was secured through laboratory guidelines, hence enabling a merge of lab systems (2014).

One limitation is that we could not address changes in severity of other poisonings through the biochemical data obtained; due to the diversity of pharmaceutical compounds in this group no unifying measures could be established. Given that time since ingestion is highly associated with plasma concentrations (Bunchorntavakul and Reddy, 2013; Lee, 2017), it would have been desirable to have data on time of ingestion. Clinical guidelines for N-acetylcysteine (NAC) treatment following paracetamol poisonings in Denmark changed in January 2013 from a 36 to a 20 h intravenous regime, implying that fewer blood tests were taken (2017b). Side-effects of NAC treatment, observed as an increase in the INR values, might limit our risk level assessment when using an INR < 1.54, though this remains disputed (Jang et al., 2013; Owens et al., 2015). Nevertheless, this limitation was equally present before and after the change in pack sizes. Furthermore, data on Anatomical Therapeutic Chemical classification (ATC) codes, number of tablets ingested and place of purchase as well as information on accessibility of drugs in the household would have been desirable. Possible confounders include extended opening hours of the Danish suicide hotline, the Lifeline (Livslinien) since January 2014.

We opted to focus on 95% confidence intervals, as these can be directly and meaningfully interpreted on the effect size scale (Tables 1 and 2).

6. Clinical implications

Universal suicide prevention strategies in the form of means restriction have been recommended as efficient in preventing deaths by suicide (Zalsman et al., 2016). Implementation of such strategies depends on public health legislation and are not straight forward to evaluate (Morthorst et al., 2018). Nevertheless, a growing body of evidence supports means restrictive efforts, ranging from limiting access to hotspots to removal of potentially toxic drugs. Seemingly, the strongest effects have been noted for suicide by jumping by restricting access and installing awareness signs and hotline numbers at hotspots (Zalsman et al., 2016). The second most efficient strategy was pack size restrictions of analgesics, associated with a 43% reduction in suicide deaths (Zalsman et al., 2016). In this study, we noted a reduction in the numbers of hospital-treated poisonings and severe poisonings as measured by specific biomarkers from national laboratory data. However, as we also found a reduction in poisonings with other drugs, it cannot be excluded that the reduction in poisonings with non-opioid analgesics was explained, at least partly, by other factors than the legislative changes. It is also possible that the legislative changes might have had an 'up-stream' public health impact observed as a general decrease in overall poisoning patterns. We therefore recommend further testing in other countries. Restrictive legislation should also include number of packages allowed in one purchase in pharmacies.

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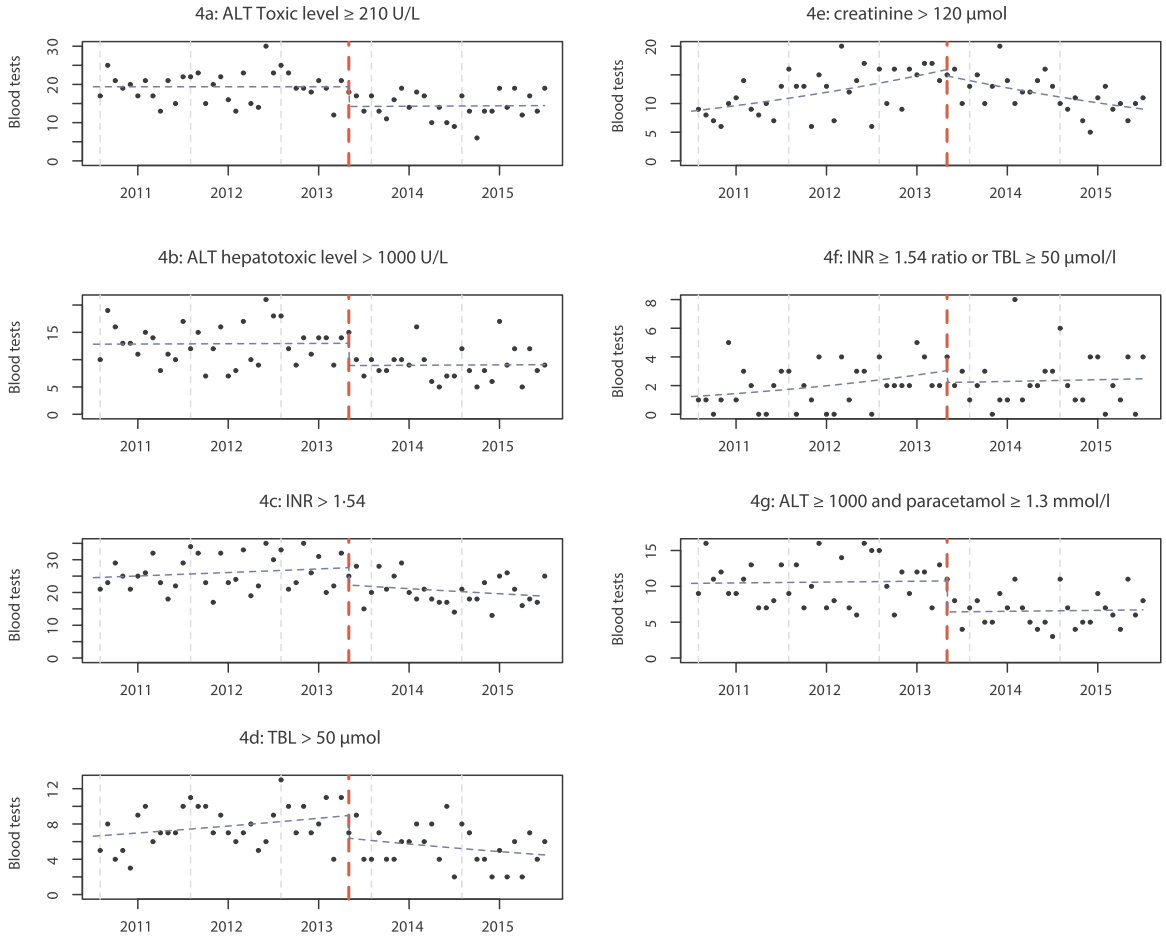

[1]The red dotted line represents the pack size restriction in September 2013.
[2]Dots represent the paek value of the given blood test measured during a hospital contact.

Fig. 4. a–g Risk levels of poisonings suggesting risk of liver injury before and after the pack size restriction 2013[1,2].

CRediT authorship contribution statement

Britt Reuter Morthorst: Formal analysis, Data curation, Validation, Conceptualization, Project administration, Writing - original draft, Writing - review & editing. **Annette Erlangsen:** Formal analysis, Data curation, Validation, Conceptualization, Project administration, Writing - review & editing. **Manon Chaine:** Formal analysis, Validation, Data curation, Writing - review & editing. **Frank Eriksson:** Formal analysis, Data curation, Validation, Writing - review & editing. **Keith Hawton:** Methodology, Validation, Writing - review & editing. **Kim Dalhoff:** Methodology, Validation, Writing - review & editing. **Merete Nordentoft:** Conceptualization, Validation, Project administration, Writing - review & editing.

Data for reference

The datasets generated during and/or analysed during the current study are partly publicly available in Denmark under Danish law and rules of the Data Protection Agency after application to Danish Health Authorities.

Declaration of Competing Interest

KH was involved in deliberations on paracetamol pack size restrictions with the UK Medicines and Health products Agency (MHRA) that led to UK legislation. We declare no other competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.02.043.

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